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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,106	10/09/2006	Morris J. Robins	49506-7	1963

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EXAMINER	
LAU, JONATHAN S	
ART UNIT	**PAPER NUMBER**
1623	

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07/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,106	ROBINS ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☒ Claim(s) *7-18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 pg / 04 Apr 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 04 Apr 2008, in which claims 2, 5 and 6 are amended to change the scope and breadth of the claim, claim 3 is amended to correct minor informalities, and new claims 7-18 are added.

This application is the national stage entry of PCT/US03/30386, filed 25 Sept 2003, and claims benefit of US Provisional Application 60/413,915, filed 25 Sept 2002, and US Provisional Application 60/416,329, filed 04 Oct 2002.

Claims 1-18 are currently pending.

Objections Withdrawn

Applicant's Amendment, filed 04 Apr 2008, with respect to the objections to the specification has been fully considered and is persuasive because the amendment corrects the identified informalities.

This objection has been **withdrawn**.

Rejections Withdrawn

Applicant's Amendment, filed 04 Apr 2008, with respect to rejections of claim 5 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been fully considered and is persuasive because the claim as

amended finds support in the section of the specification identified by Applicant, page 5, lines 5-7.

This rejection has been **withdrawn**.

Applicant's Amendment, filed 04 Apr 2008, with respect to rejections of claim 5 under 35 U.S.C. 112, first paragraph, as being indefinite has been fully considered and is persuasive because the claim as amended does not include the language that rendered the claim indefinite.

This rejection has been **withdrawn**.

The following are new or modified grounds of rejection necessitated by Applicant's Amendment, filed 04 Apr 2008, in which claims 2, 5 and 6 are amended to change the scope and breadth of the claim, claim 3 is amended to correct minor informalities, and new claims 7-18 are added.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

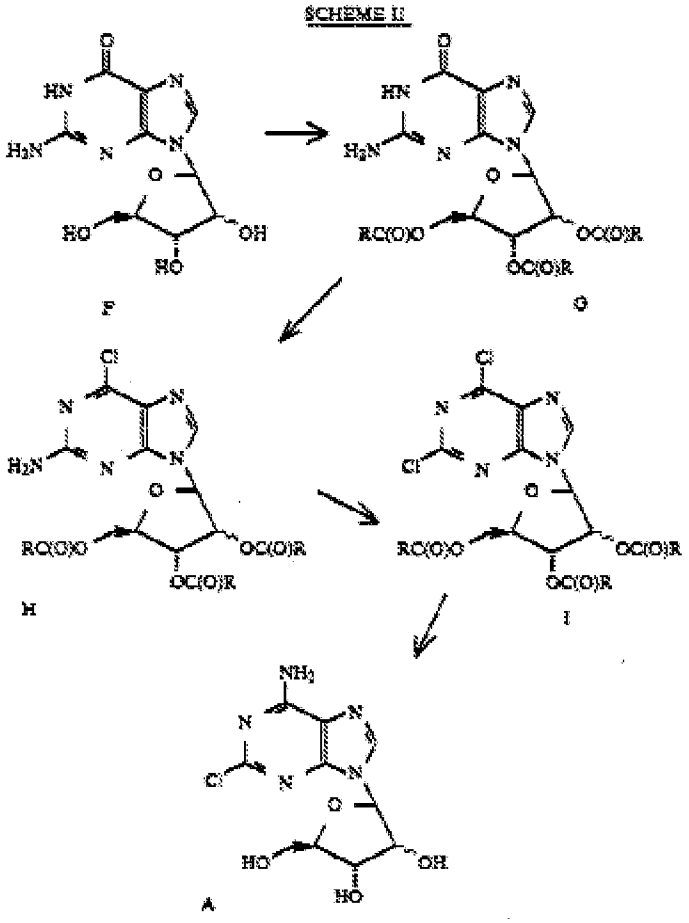
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1, 2, 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (US Patent 5,208,327, of record).

Chen discloses the reaction of guanosine wherein the hydroxyl groups of the sugar are protected with acetyl groups (see chemical structure column 2, lines 1-13) to give 2-chloroadenosine comprising the steps of reacting the 6-oxo group with an inorganic acid chloride to give the 6-chloro compound, replacing the 2-amino group with a 2-chloro group by a diazotization/chloro-dediazotization reaction using a nitrosylating agent such as an alkyl nitrite and a chloride source such as an alkyl chloride, and replacing the 6-chloro group with a 6-amino group and removing the R protecting

groups as per scheme II (column 6 lines 5-42):



See Chen, column 6 lines 56-58, 61-64, and 67. Chen discloses the conversion of the 2-chloroadenosine to the 2-chloro-2'-deoxyadenosine after conversion of the guanine moiety to a 2-chloroadenine moiety. The 6-oxo group is converted to a 6-chloro group, which is a leaving group that less reactivity than the 2-amino group in a diazotization/chloro-dediazotization reaction as evidenced by the fact the 6-chloro group remains after the diazotization/chloro-dediazotization reaction without requiring any protecting group to reduce its reactivity.

Chen does not disclose the conversion of 2'-deoxyguanosine to 2-chloro-2'-deoxyadenosine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of converting the guanine moiety to a 2-chloroadenine moiety disclosed by Chen with 2'-deoxyguanosine in place of guanosine. Chen teaches that the conversion of the guanine moiety to a 2-chloroadenine moiety may be practiced with an analog or derivative of guanosine, in particular analogs with variation at the 2' position. See Chen, column 6, lines 2-3 and 46-47. It would have been obvious to one of ordinary skill in the art at the time of the invention that it would have been simple substitution of one known element for another to obtain predictable results to practice the invention of Chen with 2'-deoxyguanosine in place of guanosine, such as by changing the sequence of adding ingredients to generate 2'-deoxyguanosine first and then converting the 2'-deoxyguanosine to 2-chloro-2'-deoxyadenosine. Both the method disclosed by Chen and the method claimed in the instant application produce the same end product, 2-chloro-2'-deoxyadenosine. Both the method disclosed by Chen and the method claimed in the instant application comprise reactions at the guanine moiety, with protecting groups affixed to the sugar moiety so that it does not react.

Response to Applicant's Remarks:

Applicant's Amendment and Remarks, filed 04 Apr 2008, have been fully considered and not found persuasive.

Applicant asserts that it would not have been obvious for one of ordinary skill in the art to practice the invention of Chen with 2'-deoxyguanosine in place of guanosine. By disclosing of analogs or derivatives of guanosine, Chen identifies that the specific functional group of 2-OH with a specific stereochemistry is not a vital characteristic of the invention. Examiner found that it would have been simple substitution of one known element for another to obtain predictable results. Lin et al. (Organic Letters, 2000, 2(22), p3497-3499, cited in PTO-892) provides evidence that, within the art of chemical transformation of nucleotide bases, (2'-deoxy or ribo)nucleosides are known in the prior art as equivalent elements known for the same purpose (page 3497, left column, paragraphs 1 and 2). An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious, see MPEP 2144.06 II.

Applicant asserts that it would not have been obvious to rearrange the steps of disclosed by Chen. However, changes in sequence of adding ingredients is *prima facie* obvious, see MPEP 2144.04 IV.C.

Applicant remarks that the order of performing process steps instantly claimed produced unexpected results in improved synthetic yields. However, the prior art examples are drawn to reaction on the scale starting with 358g 2',3',5'-O-triacetyl guanosine (column 7, line 14). The instant results are exemplified with reactions on the scale of 1.67g 3',5'-di-O-acetyl-2'-deoxyguanosine (1a) (instant specification page 13, example 1). It is well known that scale up of reactions, such as a 200x scale up when compared to the prior art, causes complications that result in a reduced synthetic yield.

See Doraiswamy (Organic Synthesis Engineering, 2001, cited in PTO-892) page 8, section Process Intensitication, "Unfortunately, although almost all of [the techniques to improve organic reactions] are known to perform very well in the chemist's lab, their scale-up to industrial size remains a daunting issue." Therefore the data indicating unexpected results are not commensurate with the scope of the claims.

Claims 3 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (US Patent 5,208,327, of record) as applied to claims 1, 2, 4 and 5 above, and further in view of Bauman et al. (US Patent 5,668,270, of record).

As recited above, Chen discloses the reaction of guanosine wherein the hydroxyl groups of the sugar are protected with acetyl groups (see chemical structure column 2, lines 1-13) to give 2-chloroadenosine with an intermediate reaction of the 6-oxo group to a 6-chloro group followed by the conversion of the 2-chloroadenosine to the 2-chloro-2'-deoxyadenosine.

Chen does not disclose the conversion of the 6-oxo group to a 6-leaving group wherein the 6-leaving group is a 6-O-sulfonyl leaving group.

Bauman et al. teaches the conversion of the 6-oxo group of guanosine to a 6-amino group with an intermediate reaction of the 6-oxo group of guanosine with a 6-O-sulfonyl leaving group, where the sulfonyl group is an alkyl or aryl sulfonyl group, in the place of the 6-halo group. See Bauman et al. column 3, lines 36-49.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of converting the guanine moiety to a 2-chloroadenine

moiety disclosed by Chen with a 6-leaving group is a 6-O-sulfonyl leaving group in the place of a 6-halo leaving group. It would have been simple substitution of one known element for another to obtain predictable results to practice the invention of Chen with a 6-O-sulfonyl leaving group in the place of the 6-halo leaving group as taught by Bauman. The methods in both references involve a similar reaction, 2-halo-adenosine produced from guanosine. Both methods comprise reactions at the 6-oxo group of a purine moiety.

Response to Applicant's Remarks:

Applicant's Amendment and Remarks, filed 04 Apr 2008, have been fully considered and not found persuasive.

The response to Applicant's remarks regarding Chen recited above is applicable to Applicant's remarks regarding Chen in view of Bauman et al.

Allowable Subject Matter

Claims 7-18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter: the limitation requiring the use of acetyl chloride and benzyltriethylammonium nitrite is free of the prior art. Chen (US Patent 5,208,327, of record) teaches a diazotization/chloro-dediazotization reaction using a nitrosylating agent such as an alkyl nitrite and a chloride source such as an alkyl chloride. The closest prior art, Francom et

al. (J. Org. Chem. 2002, 67, p6788-6796, cited in PTO-892, available online on 29 Aug 2002) teaches the diazotization-dediazoniation of aminopurine nucleosides (abstract) using of benzyltriethylammonium chloride and *tert*-butyl nitrite at -10 °C (page 6791, right column, paragraph 2). Francom et al. teaches in situ generation of NOBr or NOCl can occur (page 6790, left column paragraph 2), providing guidance to one of skill in the art that use benzyltriethylammonium nitrite and a chloride source as obvious as an equivalent known in the prior art for the same purpose as the combination of benzyltriethylammonium chloride and *tert*-butyl nitrite. However, the specific combination of acetyl chloride and benzyltriethylammonium nitrite is not obvious over the prior art of record.

Conclusion

No claim is found to be allowable as written.

Claims 7-18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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